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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,721	02/09/2004	Ralf Jockers	FRAV2003/0005USNP	9535

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,721	JOCKERS ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-17,42 and 45-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-17,42 and 45-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Exhibit A*.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 3/10/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 9/7/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 3/10/2006, claims 12-17, 42, and 45-48 are pending and currently under examination.

Claim Objections

Claim 12 is objected to because of the following informalities: The claim recites the term "iRNA." The term "iRNA" may have different meanings to those of skill in related fields and is therefore subject to misinterpretation.

For the sake of clarity and for future search purposes, it is suggested that, in the claims at the first use of the term, the term be spelled out in full to unequivocally identify what the term stands for.

Appropriate correction is required. However, Applicants are reminded of the prohibition against new matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 17, and 45–48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The claims are drawn to pharmaceutical compositions and medicinal products containing an oligonucleotide that specifically hybridizes to SEQ ID NO:21 and inhibits the expression of

OB-RGRP. Also claimed are pharmaceutical compositions and medicinal products thereof, which contain either a vector expressing the oligonucleotide or a cells containing the vector. Claim 17, and new claims 47 and 48 specifically require compositions containing "a pharmacologically active amount of a vector" or "a cell."

The "pharmaceutical composition," "medicinal product," and "pharmacologically active" language in combination with the disclosure at pages 11 and 20-23, for example, teaching that the instantly claimed interfering nucleic acids may be used to treat leptin-related diseases, requires that these claims be evaluated to determine whether the specification teaches how to use these pharmaceutical compositions and medicinal products for treating leptin-related diseases in any mammal, including humans, for example.

Problems related to the pharmaceutical use of nucleic acids were well known in the art at the time the instant application was effectively filed. Such problems include the inability to routinely deliver an effective concentration of a specific nucleic acid into a target cell, such that a target gene is inhibited to a degree necessary to produce a therapeutic effect.

Jen et al. (2000) *Stem Cells* 18:307-319 teach that

> "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive." (page 313, second column, second paragraph):

Hannon and Rossi (2004) *Nature* 431:371–378 teach that, while RNAi has the potential to be exploited therapeutically, and despite early proofs of principle, "there are important issues and concerns about the therapeutic application of this technology, including difficulties with

delivery and uncertainty about potential toxicity." (page 374, 2nd column) "Two key challenges in developing RNAi as a therapy are avoiding off-target effects and ensuring efficient delivery." (page 377, 1st column) "The issue of delivery has restricted the antisense field for almost two decades. It is feasible to infuse backbone-modified oligonucleotides *in vivo*, but achieving intracellular delivery at therapeutically effective concentrations is a major challenge. Targeted delivery to specific cell or tissue types is still not a practical reality for oligonucleotide-based therapeutics." (page 377, 2nd column) "As with HIV therapeutics, delivery of the siRNAs or shRNA vectors is the main challenge for successful treatment of HCV. The method of delivery used in several *in vivo* studies—hydrodynamic intravenous injection—is not feasible for the treatment of human hepatitis." (page 376) "However, enhancing siRNA stability is not enough unless the siRNAs can penetrate cells and tissue *in vivo* in concentrations sufficient to be therapeutically functional. As siRNAs are double-stranded molecules, delivery and cellular uptake is more of a challenge than for single-stranded antisense agents, which bind to serum proteins and are taken up by cells and tissues *in vivo*. There are a few reports of functional RNAi being obtained by systemic delivery of liposome-encapsulated siRNAs,..." (page 376) "Systemic delivery of siRNAs to T lymphocytes is probably not feasible owing to the immense number of these cells. Using viral vectors to deliver anti-HIV-encoding shRNA genes is also problematic, and systemic delivery is not yet practicable because the immunogenicity of the vectors themselves precludes performing multiple injections." (page 375)

Thus, the post-filing art indicates that the art of in vivo delivery of double stranded interfering nucleic acids for selectively inhibiting gene expression in animals and humans is unpredictable.

In view of the express teachings of the post-filing art suggesting that *in vivo* delivery of siRNA is unpredictable, it is essential that the instant application provide enabling disclosure showing how to use the invention in animals to reduce OB-RGRP expression in a cell *in vivo*.

A review of the instant application fails to find adequate representations or guidance exemplifying the use *in vivo* of the pharmaceutical preparations and medicinal products currently claimed. Although, applicants clearly discuss possible routes of delivery and methods of administration of nucleic acids (pp. 20-23), these teachings are general in nature, and do not teach the ordinary artisan how to effectively deliver siRNA or any other double-stranded nucleic acids, or combinations thereof to any target tissues and cells *in vivo* so as to effectively reduce gene expression of SEQ ID NO:21 and, thereby, OB-RGRP, to effectively treat leptin-related diseases in any subject.

Thus, the amount of disclosure is insufficient given the level of unpredictability in the art. Similarly, while the instant application is enabling for the use of double stranded nucleic acids to transfect cells in culture, it does not enable the use of these molecules *in vivo* in a way that would reasonable enable one of skill in the art to use the invention so as to obtain a desired result, e.g., a specific phenotype or outcome in an individual.

A review of the instant application finds eight (8) working examples (pp.31-39); however, these examples are directed to the delivery of antisense and siRNAs into cells *in vitro,* in cell culture, and do not directly address, represent, or demonstrate the administration and delivery of interfering nucleic acids to cells *in vivo* to specifically inhibit the expression of SEQ

ID NO:21 in cells *in vivo,* nor do these examples adequately exemplify the use of the instantly claimed oligonucleotides, vectors, and host cells to treat leptin-related diseases *in vivo.*

Put simply, the examples do not teach one of skill how to deliver these siRNAs into cells *in vivo* to treat any particular condition such as leptin-related disease, nor do they specifically show or teach one of skill how to inhibit OB-RGRP expression *in vivo.*. That is, no technical guidance or exemplary disclosure is provided regarding the use of the claimed pharmaceutical compositions and medicinal products for targeting genes in cells and tissues in living organisms, including any mammal.

As the post-filing art indicates, in culture results are not readily extrapolated to *in vivo* applications.

Given this unpredictability, the skilled artisan would require specific guidance to practice use the claimed pharmaceutical compositions to treat a leptin-related disease *in vivo* in any given patient. That is, specific guidance would be required to teach one of skill in the art how to use the claimed compositions to produce a positive effect in a patient.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teachings of the prior art does not provide that guidance, such that the skilled artisan would be able to use the claimed pharmaceutical compositions in the manner disclosed to produce the intended effects of treating the disclosed diseases.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by

the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement. Removing the "pharmaceutical," "medicinal," and "pharmaceutically active amount" language from the instant claims would overcome this rejection.

***

Claim 42 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

As amended, the claim is drawn to an iRNA oligonucleotide exhibiting at least 90% identity with one of sequences SEQ ID NO. 37 and 38, and that specifically hybridizes to SEQ ID NO:21 and inhibits expression of OB-RGRP.

The specification discloses several representative species of iRNA type, double stranded oligonucleotides, including the sense/antisense pair SEQ ID Nos 37 and 38, that specifically hybridize to SEQ ID NO:21 and/or that inhibit the expression of OB-RGRP expression.

However, the claims are directed to encompass any double stranded oligonucleotide that exhibits a minimum of 90% identity to one of SEQ ID Nos 37 and 38. Furthermore, the claims require that the recited iRNA molecules specifically inhibit OB-RGRP expression. The claims further encompass any modified double stranded molecule thereof capable of carrying out the

recited function. Thus, the claims encompass an exponential number of structurally distinct nucleic acid sequences of almost any length and base composition, limited only to the extent that they must satisfy the function recited in the claims; namely, the double stranded oligonucleotide must specifically hybridize to SEQ ID NO:21 and must inhibit the expression of OB-RGRP.

Adequate written description support under 35 USC 112, first paragraph for the entire genus of double stranded iRNA molecules now claimed in claim 42 does not exist in the instant application. The instant application discloses neither a representative number of species nor any structure/function correlation needed to satisfy the written description support for the broad genus now claimed (MPEP §2163). While the claim requires that the double stranded iRNA molecule hybridize "specifically' to SEQ ID NO:21, a defined target sequence, the limitation "hybridizes specifically" is vague and indefinite, as explained above, and does not help to describe which molecules of the hundreds of thousands now encompassed by the claim will in fact perform the intended function of inhibiting OB-RGRP expression; the limitation "hybridizes specifically" does not allow one of skill in the art to envision the structure of the iRNA nucleic acid that will inhibit OB-RGRP expression. As explained above the phrase "hybridizes specifically" is not defined by the claims or the specification.

Furthermore, in light of Applicants' remarks at page 7 rebutting the rejection of claim 12 under 35 USC §102/103, it becomes even less clear as to what does or does not consitute a specifically hybridizable iRNA molecule. For example, Applicants remarks that the "Brown sequence sports an internal mismatch and thus does not hybridize specifically for a stretch of at least 10 nucleotides" would seem to imply that there is some minimum level of complementarity below which iRNAs are no longer considered to be specifically hybridizable. However, the

instant application does not teach any such specific requirements, and provides no guidance to one of skill in the art to decide what does or does not satisfy this requirement. As a result, one of skill would be left to de novo screening to identify those particular iRNAs having at least 90% identity to one of SEQ ID Nos: 37 or 38 that also perform the intended function.

While the target sequence, SEQ ID NO:21, may provide a foundation for the design and testing of multiple numbers of iRNA molecules, one of skill in the art would, nevertheless, be left to de novo screening methods to determine whether or not a given iRNA molecule having the required level of homology with either SEQ ID NO:37 or 38 would behave in the manner required by the instant claims. That is, while the claim requires a specific minimum level of homology, the instant application makes it abundantly clear that each sequence must be experimentally tested to determine if it meets the standards set forth in the claims.

For instance, see Example 6, page 36, which teaches that antisense sequences targeting the same gene may or may not exhibit functional activity.

The claims expressly require that the iRNA molecules specifically inhibit the expression of OB-RGRP. However, the specification does not teach a correlation between this function and the structure of the iRNA molecule. As a result, one of skill in the art would not be able to envision the structure of any ds iRNA molecule or modified variant thereof that would satisfy each of these criteria.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons

of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of those specific, structurally and functionally defined iRNA molecules disclosed in the specification (such as those presently claimed in claim 42), the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of iRNA molecules that satisfy each of the criteria delineated in the claims, regardless of the complexity or simplicity of the method used to screen for such molecules. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171,

> 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.
>
> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

In the instant case, the species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

While adequate written description support exists for SEQ ID NO:37 and 38, adequate written description support does not exist for the multitude of other possible sequences having at least 90% identity to SEQ ID Nos: 37 or 38 and which also satisfy the requirements of claims 42 and 12.

Accordingly, claim 42 is rejected for lack of written description support.

Response to Arguments—Claim Rejections - 35 USC § 102/103

Claim 12 stands rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Brown et al. (US Patent 5,945,336).

Applicants argue that the cited Brown sequence contains an internal mismatch and thus does not hybridize specifically for a stretch of at least 10 nucleotides. Therefore, Applicants argue, the cited Brown sequence does not anticipate or, in the alternative, render obvious the instant claim.

Applicants' arguments have been fully considered but are not found persuasive.

A review of the cited sequence, SEQ ID NO:14, in Brown et al. shows that the cited sequence is complementary to positions 32-43 and 44-48 of SEQ ID NO:21 (see alignment, Result 20, attached as Exhibit A). Thus, the cited oligonucleotide, a 20-mer, is complementary to at least 11 contiguous nucleotides of SEQ ID NO:21. A single mismatch intercedes between flanking complementary regions spanning 11 and 5 contiguous nucleotides each. Absent evidence to the contrary, SEQ ID NO:14 is considered to have sufficient compplementarity to hybridize specifically to SEQ ID NO:21, as now claimed.

Furthermore, Applicants are reminded that the instant claims do not require that the oligonucleotide specifically hybridize "for a stretch of at least 10 nucleotides," nor is there any disclosure in the specification teaching that "hybridizes specifically" strictly means that the oligonucleotides must specifically hybridize "for a stretch of at least 10 nucleotides."

Absent a clear, limiting definition, either in the specification or the claim, the phrase "hybridizes specifically" is considered to impart significant breadth to the instant claim. The instantly cited reference is considered to teach an oligonucleotide within the scope of the instant invention.

Thus, the invention as now claimed remains rejected as anticipated by, or, in the alternative, as obvious over Brown et al.

Response to Arguments—Claim Rejections - 35 USC § 103

Claims 12–17 and 45–48 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bailleul et al. (US Patent Application 2003/0166847); Agrawal and Tang (WO 94/01550); Taylor et al. (1999) *Drug Discovery Today* 4:562–567; Bennet et al. (US Patent 5,998,148); and Baracchini et al. (US Patent 5,801,154).

Claims 12 and 13 are drawn to a single or double stranded interfering RNA, comprising from 10 to 60 nucleotides, which hybridizes specifically to polynucleotide sequence SEQ ID NO:21 and which inhibits expression of OB-RGRP. Dependent claims 14 and 15 are drawn to vectors and cells thereof. Amended claims 16 and 17 are drawn to medicinal products and pharmaceutical compositions thereof, comprising the oligonucleotide. New claims 45-48 are drawn to medicinal products and pharmaceutical compositions, thereof containg vectors and host cells.

Applicants argue that Bailleul et al. teach antisense molecules against the 5' sequences of SEQ ID NO:21, not 3' sequences. Accordingly, Applicants argue, Bailleul et al. teaches away from the invention. Applicants argue that Agrawal teaches hairpin DNA against HIV only and does not teach or suggest the invention. Applicants argue that Taylor does not teach RNAi for therapy. Applicants argue that Bennet and Baracchini fail to teach or suggest the instant invention.

Applicants' arguments have been fully considered but are not found persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Additionally, in attacking each of the references, Applicants argue limitations that are not specifically claimed.

Applicants are reminded that the instant specification defines iRNA molecules at pages 8-9 as follows:

> "These iRNAs may be double-stranded, in which case they advantageously consist of two strands comprising from 15 to 60 nucleotides."
>
> "The iRNAs may also be expressed in single-stranded form. Such iRNAs may then comprise a loop. They advantageously comprise from 15 to 60 nucleotides."

The prior art applied in this rejection clearly discloses and fairly suggests the design, preparation, and application of molecules meeting these criteria.

Specifically, the references as a whole teach double-stranded, hairpin, RNA, DNA, and RNA/DNA molecules, vectors, host cells, and pharmaceutical compositions thereof, having complementarity to SEQ ID NO:21.

Agrawal et al. disclose self-stabilized, hairpin oligonucleotides that comprise the presence of two structural features: a target hybridizing region and a self complementary region (pg. 5, lines 13-17) that can be polymers of ribonucleotides (pg. 8, lines 10-12) that form a double stranded structure that is resistant to nucleolytic degradation (pg. 5, lines 25-30). Agrawal et al. disclose that the target hybridizing region is from about 8 to about 50 nucleotides in length (pgs. 9-10), that the self complementary region can span the target hybridizing region, that the complementary sequences form base pairs resulting in a hairpin structure and that the intramolecular base pairing can be so extensive as to involve every nucleotide of the

oligonucleotide (pg. 15). Fig. 5, cmpd C, for example, shows a fully complementary hairpin, expression-inhibiting hairpin oligonucleotide having a double stranded region spanning 17 bases. Agrawal et al. also explicitly teach that the target hybridizing and a self complementary regions of the oligonucleotide can be composed of ribonucleotides, deoxyribonucleotides, or both, with ribonucleotide and/or deoxyribonucleotide monomers being connected together via 5' to 3' linkage (pages 8-16, for example). Accordingly, Agrawal et al. teach hairpin RNAs having sense and antisense regions for inhibiting gene expression in cells *in vitro* and *in vivo.* Also disclosed are pharmaceutical compositions for administering the hairpin oligonucleotides to cells in animals (page 18, for example).

Absent evidence to the contrary, these molecules have the characteristic features of an interfering RNA nucleic acid molecule, as now defined by the specification.

While Agrawal et al. may exemplify certain embodiments for inhibiting viral replication, the disclosure, taken as whole, provides a general blueprint for the preparation of hairpin antisense molecules, comprising self-complementary sense and antisense regions, which are said to have the capability for inhibiting gene expression in a cell.

Any inherent properties of the self-stabilized oligonucleotides taught by Agrawal et al., such as their ability to facilitate RNAi, not specifically recognized at the time the prior art document was published, are not considered to limit the application of this art to the instant claims, since the property is simply a latent characteristic of the hairpin oligonucleotides disclosed by Agrawal. The molecules clearly meet the structural requirements of the instantly claimed iRNA molecules.

With regard to Bailleul et al., Taylor et al. Bennet et al., and Baracchini et al., these references are relied on as a whole for what they taught or fairly suggested to one of skill in the art at the time at the time the instant invention was made.

While it may be true that Bailleul et al. teach targeting 5' sequences in SEQ ID NO:21, the instant claims do not currently exclude or recite any limitations as to the target regions of SEQ ID NO:21. And while it may be true that Taylor et al. Bennet et al., and Baracchini et al. pertain primarily to antisense technology, their teachings are relied on for what they suggested and taught regarding the design, preparation, and application of any antisense molecule, including the self-stabilized, double stranded molecules taught by Agrawal et al. and Tang et al. to inhibit gene expression, either for research purposes to elucidate the function of a gene such as SEQ ID NO:21, or for clinical purposes to treat a disease.

MPEP §2144 states in part that "It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972)."

The instant claims do not specifically require that the iRNA oligonucleotides be used for clinical purposes only, nor do they exclude the application of oligonucleotides for research, *in vitro*, studies.

With regard to the claimed vectors and host cells, Bailleul et al. teach that Methods which are well known to those skilled in the art can be used to construct recombinant vectors which will express antisense polynucleotides of the gene encoding LRGRP (paragraph 130). They also teach that such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, antisense cDNA constructs that

synthesize antisense RNA constitutively or inducibly can be introduced into cell lines, cells or tissues (paragraph 136). Bailleul et al. also teach the preparation of pharmaceutical compostions at paragraph 12, for example).

Accordingly, the instant claims stand rejected as obvious over the instantly cited references.

Response to Applicants' Arguments

Applicants' arguments presented on 3/10/06 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on Mon–Fri, 8:00 am–4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Peter Paras, can be reached at telephone number 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval system (PAIR). Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Louis V. Wollenberger, Ph.D.
Examiner
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